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META-ANALYSIS

Ophthalmic adverse drug reactions: A nationwide detection using hospital databases

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Abstract

AIM: To detect ophthalmic adverse drug reactions (ADRs), that occurred in Portugal from 2000 to 2009, through the utilization of administrative hospital databases. We also intended to compare the results of this methodology with spontaneous reporting.

METHODS: We conducted a retrospective nationwide study using hospital administrative databases, which included all inpatients and outpatients in all public hospitals in Portugal, from 2000 to 2009. We used International Classification of Diseases - 9th Revision - Clinical Modification (ICD-9-CM) coding data that allowed the detection of ADRs. We used WHO's definition for ADR. We searched all of ICD-9-CM terms in Ophthalmology for codes that included "drug-induced", "iatrogenic", "toxic" and all other that could signal an ADR, such as "362.55 - toxic maculopathy" or "365.03 - steroid responders", and also "E" codes (codes from E930 to E949.9, that exclude intoxications and errors).

RESULTS: From 11944725 hospitalizations or ambulatory episodes within that period of time, we identified 1524 probable ophthalmic ADRs (corresponding to a frequency of 1.28 per 10000 episodes) and an additional 100 possible ophthalmic ADRs. We used only 4 person-hours in the application of this methodology. A total of 113 spontaneous reports arose from ophthalmic ADRs from 2000 to 2009 in Portugal (frequency of 0.095 per 10000 episodes).To our knowledge, this was the first estimate of the frequency of ophthalmic ADRs through the use of databases, and the first nationwide estimate of ophthalmic ADRs, in Portugal. We identified 1524 probable ADRs and 100 possible ADRs.

CONCLUSION: This database methodology adapted for Ophthalmology may represent a new approach for the detection of ophthalmic ADRs, since these codes exist in the ICD-9-CM classification. Its performance was clearly superior to spontaneous reporting.

Key words: Adverse drug reactions; Ophthalmology; Ocular; Databases; Pharmacovigilance

Core tip: We used International Classification of Diseases - 9th Revision - Clinical Modification coding data for the detection of adverse drug reactions (ADRs). From 11944725 episodes, we identified 1524 probable ophthalmic ADRs. 113 spontaneous reports arose from that population. This was the first nationwide study of ophthalmic ADRs and may represent a new Pharmacovigilance approach, with a higher detection than spontaneous reporting.

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INTRODUCTION

Adverse drug reactions (ADRs) are responsible for significant morbidity, mortality and costs in Health Care systems[1]. They may occur in 16.9% of patients during hospitalization (95%CI: 13.5-20.2)[2] and provoke 5.3% of hospital admissions (interquartile range 2.7%-9.0%)[3]. ADRs are a frequent cause of death in developed countries[4]. However, in Ophthalmology the evidence is scarce and lacks systematization[5]. A review about challenges in ADRs in Ophthalmology[5] concluded that there are several areas that can be improved, namely by applying always the definition of ADR of the World Health Organization (WHO)[6], by performing a causality assessment in each ADR (which determines the probability of representing a true ADR; the most utilized causality assessments of ADRs are from WHO[7] and from Naranjo *et al*[8]).

The development and validation of new methodologies for an improved detection of ADRs would be another area of improvement[5,9]. There are Pharmacovigilance methodologies[9] used for the detection of ADRs and that can be adapted for detecting ADRs in Ophthalmology, but they may have methodological issues: Spontaneous reporting is the most used (it needs low resources) and is the only Pharmacovigilance method continuously used in the majority of countries, being the main support of WHO International Drug Program. However, it has several limitations, namely, the smallest detection rate of several Pharmacovigilance methods[10], under-reporting[11], heterogeneous report quality[12] and increased risk of bias[12]. Intensive and prospective monitoring are methodologies with good detection rates but too resource-consuming for continuous application[13].

Administrative hospital databases have large clinical information and thus may represent an interesting Pharmacovigilance approach with readily available and cheap information[10]. Some authors have utilized databases[10,14] for the detection of ADRs, taking advantage of the large quantity of clinical information readily available, containing coding data that can be used as an alert for the detection of an ADR, with low relatively low resources required.

Our purpose was to identify and characterize ophthalmic ADRs in a Nationwide study in Portugal, using hospital databases with clinical information.

MATERIALS AND METHODS

Study design

A retrospective study was performed for ADR identification using hospital administrative databases with information from all public hospitals in Portugal, from 2000 to 2009, obtained from our National Health Department (data from the second semester of 2009 was not available). These databases contain anonymized data for patient identification, episode and process number, and also information on age, sex, admission date, discharge date, ward(s), hospital attended (tertiary, university), area of Healthcare, district, outcome (death, discharge, transfer), payment data and International Classification of Diseases - 9th Revision - Clinical Modification (ICD-9-CM)[15] codes for: diagnoses (principal diagnosis, other diagnosis up to 19), procedures (up to 20) and external causes (up to 20). Patient population included all patients hospitalized or admitted for ambulatory care, in all public hospitals in Portugal, from 2000 to 2009 (inpatients and outpatients). All investigations were performed according to the guidelines of the Declaration of Helsinki and Institutional Review Board approval from was obtained.

Definition of ADR

There is some misuse of terms in this matter; therefore we present definitions.

An ADR[6] is: "any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy". Therefore, to increase specificity, we wanted to assess only ADRs. Adverse drug event is not a synonym of ADR. There are other definitions of ADR, namely from Karch *et al*[16] and from Edwards *et al*[17], but we used the definition of WHO. An adverse event[18] is: "an injury related to medical management (all aspects of care, including diagnosis and treatment, failure to diagnose or treat, and the systems and equipment used to deliver care), in contrast to complications of disease". An adverse drug event[19] is: "An injury related to the use of a drug, although the causality of this relationship may not be proven". These include medication errors (namely the prescription of a wrong dose) and ADRs. We aimed to assess strictly ADRs.

Detection of ADRs

Hospital administrative databases include information of diagnosis. Codes searched for ADR identification were adapted to the specificities of Ophthalmology and resulted from a thorough search of: all terms of ICD-9-CM in Ophthalmology that included "drug-induced", "iatrogenic", "toxic" and all codes that could signal an ADR, such as "362.55 - toxic maculopathy" or "365.03 - steroid responsers", as detailed in the Results Section.

We also performed a search of general ADRs through the use of 'E' codes (ICD-9-CM codes from E930 to E949.9, designed to represent ADRs and already excluding wrong doses, errors and intoxications) to assess if these general ADRs could detect ophthalmic ADRs.

In this study, we performed a query of Ophthalmology in a nationwide study using administrative databases, including inpatients and ambulatory patients. Our main outcome was ADR detection. Secondary outcomes included: type of ADR, age, sex, admission diagnosis, other diagnoses, hospital length-of-stay and year of discharge. We performed WHO's causality assessments of ADRs,

with two independent reviewers. Differences were resolved by consensus. A third review was consulted to help resolved differences. We also registered how many person-hours were spent in the application of this methodology, to estimate cost (resources spent). The number of person-hours refers to the number of hours and number of people used in the application of this methodology; commonly used in the comparison of different Pharmacovigilance methodologies[19]. The number of spontaneous reporting of ADRs in hospitalized patients from 2000 to 2009 was obtained from Portuguese National Authority of Medicines (INFARMED), for comparison[20].

Statistical analysis

Statistical analyses were done using the χ^2 test for categorical variables (or exact Fisher's test whenever possible), Student's *t*-test for normally distributed continuous variables and Mann-Whitney or Kruskal-Wallis for variables without normal distribution, using SPSS v20. The a priori level of significance was $P < 0.05$.

RESULTS

Study population

There were 11944725 patients hospitalized or with ambulatory episodes in public hospitals of Portugal, from 2000 to the first semester of 2009. The baseline characteristics of the study population (n = 11944725) are shown in Table 1. The mean age of hospitalized patients was 48 ± 27 years and in 55.2% of episodes the patient was female. We spent only 4 person-hours in the application of this methodology.

From 2000, there was a slight increase in the number of hospitalizations in Portugal. Specific ophthalmic ADRs (n = 1524) were detected through the search of codes that could represent particular ophthalmic ADRs, as shown in Table 2. This corresponds to a frequency of 1.28 ophthalmic ADR per 10000 episodes. Additionally, 100 episodes that could possibly correspond to an ophthalmic ADR were also detected (Table 2). Therefore, a total of 1624 possible ophthalmic ADRs were detected. These possible ADRs included: conjunctival concretions, pigmentations and deposits (which can be caused by drugs such as topical adrenaline[21], but also by other factors, therefore may correspond to an ADR in some cases) and acquired color vision deficiencies (which may be caused by drugs such as sildenafil[22], but have other non related causes).

The search of general ADRs through the use of "E" codes allowed us to identify 116720 ADRs, but only 62 of them corresponded to the ophthalmic ADRs that were identified.

The total number of spontaneous notifications of ADRs in Portugal from 2000 to 2009 was 13562, from which 113 were spontaneous reports specific of ophthalmic ADRs. There were 553 additional spontaneous reports of systemic ADRs that included some ophthalmic manifestations.

Table 1 Socio-demographic characteristics of study population

Characteristic	Value
Number of episodes (inpatient, ambulatory)	11944725
Mean age (yr, mean ± SD)	48 ± 27
Female gender n (%)	6598266 (55.2)
District with higher number of hospitalizations	1st: Lisbon 21.2% 2nd: Oporto 17.2% 3rd: Setubal 7.66%
Mean hospital length-of-stay for inpatients (d, mean ± SD)	7.1 ± 3.21
Number of probable ophthalmic ADRs	1524

ADRs: Adverse drug reactions.

Table 2 Clinical codes searched and respective results in the portuguese database

ICD-9-CM code	Diagnosis	No. of episodes
Specific ophthalmic ADR codes		
362.55	Toxic maculopathy	1388
365.03	Steroid responders	4
365.31, 365.32	Corticosteroid-induced glaucoma	0
364.55	Miotic pupillary cyst (provoked by pilocarpine)	2
364.81	Floppy iris syndrome	2
366.45	Toxic cataract	83
367.89	Other drug-induced disorders of refraction and accommodation, Toxic disorders of refraction and accommodation	25
377.34	Toxic optic neuropathy, Toxic amblyopia	20
Possible signs of ophthalmic ADRs		
366.46	Cataract associated with radiation and other physical influences	10
372.54	Conjunctival concretions	67
372.55	Conjunctival pigmentations, including conjunctival argyrosis	
372.56	Conjunctival deposits	
368.55	Acquired color vision deficiencies	23
368.59	Other color vision deficiencies	
	Sub-Total specific	1524
	Total	1624

ICD-9-CM: Classification of Diseases - 9th Revision - Clinical Modification; ADRs: Adverse drug reactions.

DISCUSSION

To our knowledge, this is the first estimate of the frequency of ophthalmic ADRs through the use of administrative databases, and the first to apply a nationwide estimate of ophthalmic ADRs, in Portugal. We identified 1524 probable ADRs and 100 possible ADRs. This may represent a new approach for the detection of ophthalmic ADRs, since these codes exist in the ICD-9-CM classification.

The strengths of our study include: our comprehensive database, which contains data from all hospitalizations and ambulatory episodes in every public hospital in Portugal within almost a decade, the fact that this is a new methodology to aid ADR detection (until now only case reports and spontaneous reports were available for

ADR detection), and the fact that these codes are widely available and universal, making possible to easily build estimates of ophthalmic ADRs in other countries and other years. In fact, it would be very interesting to see if ophthalmic ADRs in Portugal have the same distribution, frequency and characteristics in comparison with other countries, therefore further studies are necessary.

Limitations of our work are inherent to the use of administrative databases, which may contain incomplete or wrong data and coding bias[23] (in which coders select a different code to increase reimbursement to their hospital). The small number of ADRs found may be considered a limitation, but on the other hand this is a methodology resource-sparing (only 4 person-hours spent in its application), having potential for widespread application in other countries. Also, this method identified 1524 probable ADRs, a much higher number than the number of ophthalmic ADRs found by spontaneous reporting: 113.

We suggest complementing spontaneous reporting with this database methodology to increase detection of ophthalmic ADRs. In fact, the complementary use of several methodologies is defended by several authors[24], in order to enhance ADR detection and increase patient safety. Finally, we believe that after this study, these codes should be applied prospectively in a future study in a nation-wide basis, enabling an expert to confirm each ADR and causing drug, to further complete and validate the data suggested here, and to integrate this method as a Pharmacovigilance methodology.

In conclusion, Ophthalmology represents simultaneously a challenge and an opportunity to identify ADRs. This is the first nationwide estimate of ophthalmic ADRs. Administrative databases are a useful methodology for the detection of ocular ADRs, but require adapted diagnoses codes. They may underestimate the real number of ADRs, but nevertheless they have the potential to complement spontaneous reporting as a methodology for ophthalmic ADR detection, with a higher detection rate.

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COMMENTS

Background

Adverse drug reactions (ADRs) are a frequent cause of death in developed countries. However, in Ophthalmology the evidence is scarce and lacks systematization.

Research frontiers

There are Pharmacovigilance methodologies used for the detection of ADRs and that can be adapted for detecting ADRs in Ophthalmology, but they may have methodological issues.

Innovations and breakthroughs

This is the first estimate of the frequency of ophthalmic ADRs through the use of administrative databases, and the first to apply a nationwide estimate of ophthalmic ADRs, in Portugal.

Applications

The authors suggest complementing spontaneous reporting with this database methodology to increase detection of ophthalmic ADRs.

Peer review

This is a well written article reporting the adverse effects of ophthalmic drugs. The methods are well described, and the results are easy to understand.

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